

OBSERVATIONS ON THE PHARMACOLOGY OF
MITRAGYNINE

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INTRODUCTION

The leaves of *mitragyne speciosa*, called by the natives Kratom, are much used in the Peninsula of Siam, and to a smaller extent in Bangkok, as a habit drug. The fresh leaves are, for the most part, chewed by the natives, but in some cases, the dried leaves are smoked.

The alkaloid, Mitragynine, was first isolated and named by Field (1). She gave it the formula $C_{22}H_{31}O_5N$. The substance is probably an indole derivative, containing three methoxy-groups; it contains an ester grouping, and its formula is probably $C_{17}H_{22}N(OMe)(COO Me)_2$. There is little clear information as to the effects produced by prolonged use of the drug. Some claim that the addicts are thin, with distended stomachs, unhealthy complexions, dark lips, and dry skin. The main symptoms of acute overdosage are vomiting and vertigo. Numbness, muscular twitchings, and certain indefinite cardiac symptoms have been reported. As will be seen, the pharmacological actions of the drug are in some respects like those of quinine, but in addition it has a rather special effect on the autonomic system and on the medulla. The supply of Mitragynine fumarate and Mitragynine acetate, which were the salts used for this investigation, were provided through the kindness of Professor G. Barger and the Chemotherapy Committee of the Medical Research Council.

ACTION ON SIMPLE ORGANISMS

Mitragynine at 1:10,000 dilution kills paramoecia in thirty minutes. Death is preceded by a stage of increased movement



and is not followed by disintegration of the protozoal bodies. In table 1 there are compared the actions of Mitragynine fumarate and quinine bihydrochloride. In table 2 are compared the effects of rather stronger concentrations of these same drugs. The fact that death was not followed by disintegration in the case of Mitragynine salts, while quinine not only kills the animals, but

TABLE 1

Showing the effect of different dilutions of Mitragynine fumarate and quinine bihydrochloride on paramoecia in 24 hours

CONCENTRATION OF THE DRUG USED	MITRAGYNE FUMARATE	QUININE BIHYDROCHLORIDE
1:20,000	Dead	Dead
1:40,000	Dead	Dead
1:50,000	Dead	Few alive
1:66,000	Dead	About half the number alive
1:100,000	Dead	Alive; few dead
1:200,000	Few alive	Alive

TABLE 2

Comparative effects of Mitragynine fumarate and quinine bihydrochloride in higher concentrations on paramoecia

CONCENTRA- TION OF THE DRUG	MOVEMENTS SLUGGISH; TIME		DEATH; TIME		DISINTEGRATION OF BODIES	
	Mitragynine	Quinine	Mitragynine	Quinine	Mitragynine	Quinine
	<i>minutes</i>	<i>minutes</i>	<i>minutes</i>	<i>minutes</i>		
1:2,000	$\frac{1}{2}$	1	5	5	No	Yes
1:4,000	1	3	7	6	No	Yes
1:7,000	2	4	15	11	No	Yes
1:10,000	2	10	30	18	No	Yes
1:20,000	7	20	60*	60	No	Yes

* Few alive.

also causes rapid disintegration of their bodies, prompted the writer to compare the effect of other substances on paramoecia. Asphyxia by nitrogen gas causes death in about three and one-half hours, and there is no disintegration. Treatment with H_2S kills the animals in twenty minutes and again there is no disintegration. Potassium cyanide at a dilution of 1:200 kills in two minutes, and death is followed by rapid disintegration of the cells.

ACTION OF MITRAGYNINE ON BACTERIA AND TRYPANOSOMES

Table 3 shows the effects of various concentrations of Mitragynine on the growth of staphylococcus and *B. coli* respectively. It will be seen that growth is not inhibited in dilutions of the drug lower than 1:330. Mitragynine has no observable curative action on mice infected with *Trypanosoma equiperdum*.

THE EFFECTS OF MITRAGYNINE ON CELL OXIDATION SYSTEMS

Quinine, KCN, and H_2S are known to inhibit certain cell oxidation systems. The action of Mitragynine upon (a) the total oxygen uptake by tissue cells, (b) the indophenol oxidase system, and (c) the dehydrase system, was investigated upon the lines and

TABLE 3

Showing the action of Mitragynine fumarate on the growth of Staphylococcus albus and Bacillus coli

CONCENTRATION OF MITRAGYNINE	GROWTH OF STAPHYLOCOCCUS		GROWTH OF <i>B. COLI</i>	
	After 24 hours	After 48 hours	After 24 hours	After 48 hours
1:250	No growth	No growth	No growth	No growth
1:330	No growth	Growth	No growth	No growth
1:500	No growth	Growth	Growth	Growth
1:1,000	No growth	Growth	Growth	Growth
1:2,000	Growth	Growth	Growth	Growth

by the methods of Keilin (2). Suspensions of liver cells (guinea pig) were put up in Barcroft's apparatus and the oxygen uptake determined in the presence and absence of Mitragynine fumarate 0.05 per cent and quinine hydrochloride 0.05 per cent. Figures 1 and 2 are graphical representations of results of two experiments. It will be seen that the oxygen uptakes of the cells are inhibited by both drugs, and that Mitragynine is the more powerful of the two. Preparations were next made according to the directions of Keilin for the study of the indophenol oxidase system. Each apparatus contained liver emulsion, paraphenylenediamine, and equivalent amounts of quinine, Mitragynine, or Ringer's solution, as the case might be. Figures 3 and 4 show the results obtained. Again, both quinine and Mitragynine inhibit the action of the

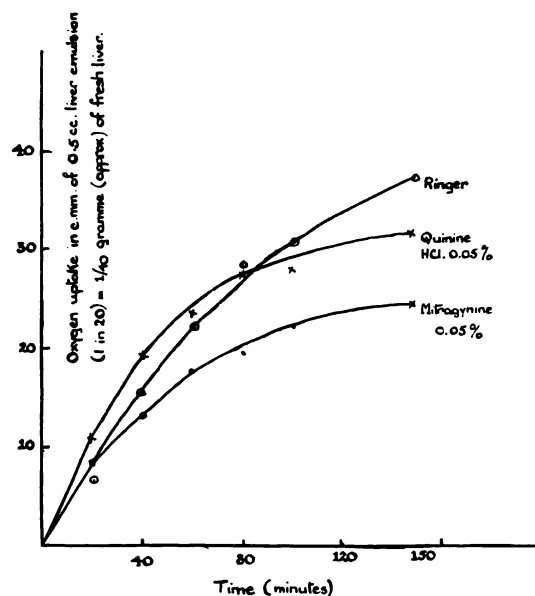


FIG. 1. SHOWING THE EFFECT OF QUININE HYDROCHLORIDE 0.05 PER CENT AND MITRAGYNINE FUMARATE 0.05 PER CENT ON OXYGEN UPTAKE ON $\frac{1}{10}$ GRAM OF FRESH LIVER

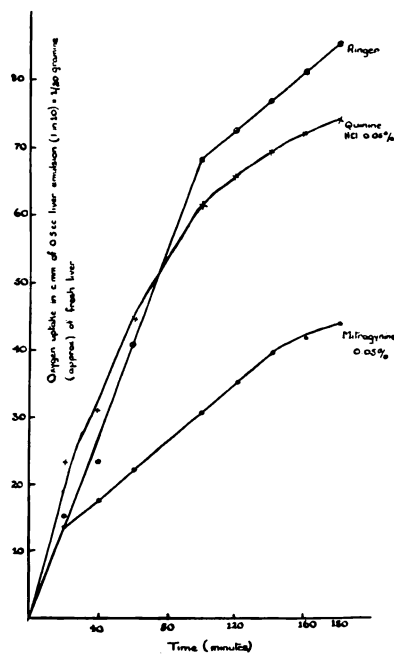


FIG. 2. SHOWING THE EFFECT OF QUININE HYDROCHLORIDE 0.05 PER CENT AND MITRAGYNINE FUMURATE 0.05 PER CENT ON THE OXYGEN UPTAKE OF $\frac{2}{10}$ GRAM OF FRESH LIVER

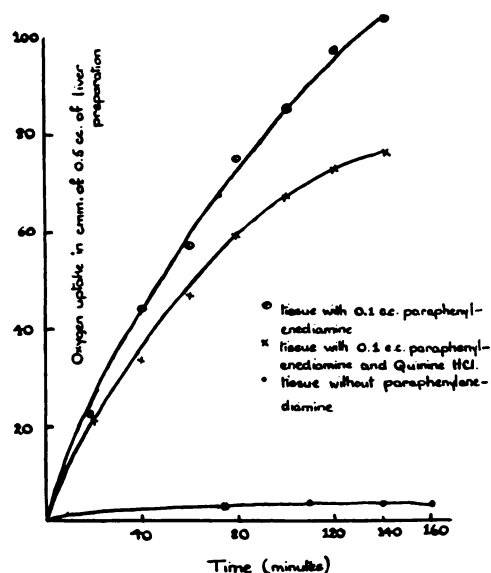


FIG. 3. EFFECT OF QUININE HYDROCHLORIDE 0.05 PER CENT ON INDOPHENOL OXIDASE OF RABBIT'S LIVER

Curve (upper and middle) represent the oxygen uptake of the suspension at 37°C. in the presence of paraphenylenediamine. Lower curve shows the oxygen uptake of the suspension without the reagent.

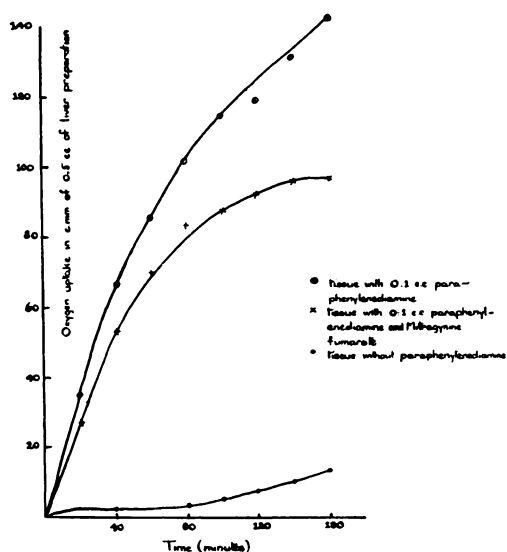


FIG. 4. EFFECT OF MITRAGYNE FUMARATE 0.05 PER CENT ON INDOPHENOL OXIDASE OF RABBIT'S LIVER

Curve (upper and middle) represent the oxygen uptake of the suspension at 37°C. in the presence of the reagent paraphenylenediamine. Lower curve shows the oxygen uptake of the suspension without the reagent.

indophenol oxidase system. Finally, the dehydrase systems were studied. Table 4 shows that these systems also are inhibited by Mitragynine. Urethane, a drug which is well known to depress the activity of these systems, was used as a control. It is clear from these experiments that Mitragynine is a pronounced general depressant of cellular oxidations, and that both indophenol oxidase and dehydrase systems are affected.

ACTION OF MITRAGYNINE ON PLAIN MUSCLE TISSUE

1. Isolated intestine

The action of Mitragynine on the isolated intestine was determined by Magnus's method, and it was found that solutions of

TABLE 4

	REDUCTION TIME OF METHYLENE BLUE							
	Experiment I	Experiment II		Experiment III		Experiment IV		Experiment V
	a	b	a	b	a	b		
	min- utes	min- utes	min- utes	min- utes	min- utes	min- utes	min- utes	min- utes
Ringer	44	43	24	33	15	8	9	15
Urethane, 5 per cent	69	76			Over 60	10	14	26
Mitragynine fumarate, 0.0133 per cent	45		50	54	21	9	12	24

In experiments II, III and IV, after noting the time of reduction (a), the air was allowed in, the contents were shaken vigorously till blue colour was restored. The tubes were evacuated again and the reduction time again noted (b).

1:20,000 to 1:100,000 caused a decrease in the amplitude of movements and a diminution of the tone of the muscle. The effects were characteristic of a depressant action on the preparation (see fig. 5).

2. Intact intestine

The effect of Mitragynine on intestinal movement was investigated in deccbrate animals. The movements were recorded by the balloon method. Mitragynine was given intravenously in doses of 15 to 20 mgm. Cats were employed for the experiments. Figure 6 shows one of the typical tracings obtained. It was

observed that Mitragynine lowers the threshold of the intestine to stimulation of the vagus. Usually, for instance, excitation of

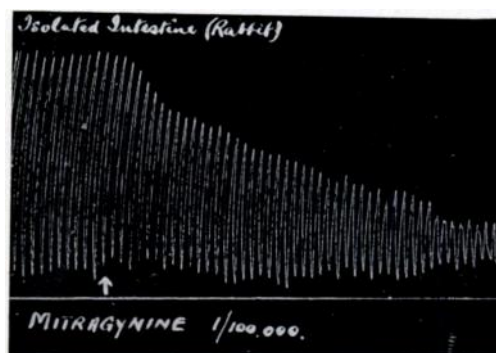


FIG. 5. SHOWING THE EFFECT OF MITRAGYNINE FUMARATE IN DILUTION OF 1:100,000 ON RABBIT'S ISOLATED INTESTINE

Time, 1 cm. = 46.0 seconds

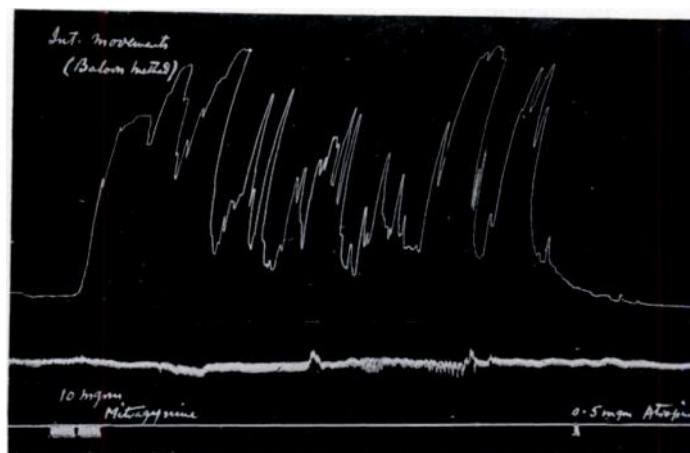


FIG. 6. CAT; PITHED; BLOOD PRESSURE; INTESTINAL MOVEMENTS (BALLOON METHOD). SHOWING THE EFFECT OF 10 MG. OF MITRAGYNINE AND 0.5 MG. OF ATROPINE ON MOVEMENTS OF THE INTESTINE

Time, 1 cm. = 32 seconds

the peripheral end of the cut vagus with a faradic current, causes only feeble movements of the intestine. If, however, 10 to 15 mgm. of Mitragynine are administered, such stimulation be-

comes at once effective. Administration of atropine completely abolishes the stimulating effects of Mitragynine. Since Mitragynine does not cause increased movements in the isolated intestine, and since, in the intact animal, its effects are abolished by atropine, it is not likely to act directly on muscle fibers. Similarly, in view of the fact that it relaxes the isolated intestine, it is not probable that it acts directly on the vagus nerve endings. By

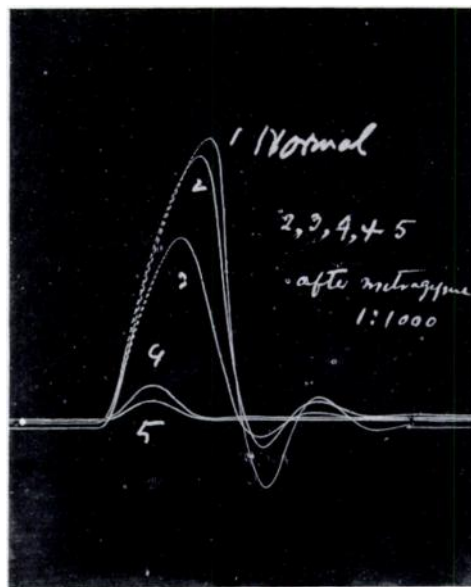


FIG. 7. CONTRACTION CURVES OF HYOGLOSSAL MUSCLE, STIMULATED BY BREAK SHOCK. SHOWING THE EFFECT OF DROPPING 1:1000 SOLUTION OF MITRAGYNE FUMARATE

1, normal; 2, one minute after; 3, four minutes after; 4, ten minutes after; 5, fifteen minutes after.

a process of elimination, we must conclude that the action of Mitragynine on the alimentary canal is due to excitation of the autonomic ganglion cells.

3. Uterus and bladder

The action of Mitragynine on the isolated uterus is similar to that on the isolated intestine. On the fully relaxed horn of a

guinea pig's uterus, Mitragynine has no effect; but if contraction is induced by any of the oxytocic drugs, Mitragynine induces immediate relaxation. Similar effects were obtained on strips of rabbit's bladder.

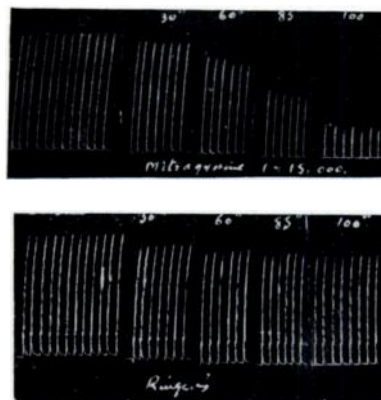


FIG. 8. CONTRACTION CURVES OF TWO GASTROCNEMII MUSCLES FROM THE SAME FROG

The upper shows the effect of 1:15,000 Mitragynine in Ringer's solution in a Lucas trough. The lower is the control in Ringer; break shocks were passed through the muscles every ten minutes for two hours. Shows the height of contraction at 30 minutes, 60 minutes, 85 minutes, and 100 minutes.



FIG. 9. FATIGUE CURVE OF TWO SARTORIUS MUSCLES FROM THE SAME FROG

Upper, control in Ringer. Lower 1:80,000 Mitragynine. Time, 1 cm. = 85 seconds.

4. *Striped muscle*

Figure 7 shows the effects of Mitragynine on the contraction of the hyoglossus muscle of the frog. It will be seen that there is a

progressive fall in the power of muscle contraction. Figure 8 shows the effect of the drug on the excitability of the frog's gastrocnemius muscle. The excitability falls continuously with time. Figure 9 shows that the frog's sartorius and is fatigued more rapidly in the presence of Mitragynine than in its absence.

EFFECT ON THE HEART AND CIRCULATION

For these investigations, the animals used were frogs, rabbits, and cats. The frog's heart, perfused through the hepatic vein with a solution of Mitragynine, showed a depression of contrac-

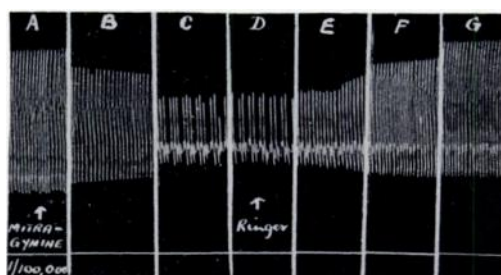


FIG. 10. RECORD OF CONTRACTION OF THE FROG'S HEART PERFUSED THROUGH THE HEPATIC VEIN WITH A SOLUTION OF MITRAGYNINE FUMARATE 1:50,000 IN RINGER SOLUTION

A, Ringer only; at arrow Mitragynine solution perfused; B, after four minutes; C, after fifteen minutes; D, after eighteen minutes. At the second arrow the fluid was changed to Ringer. E, after twenty minutes; F, after twenty-three minutes and G, after twenty-six minutes. Time, 1 cm. = 49.2 seconds.

tion which disappeared on perfusing the organ again with ordinary Ringer's solution. A similar effect was observed when the isolated rabbit's heart was perfused. It was found, in addition, that the outflow from the coronary vessels was increased by about 25 per cent by the administration of the drug. Perfusion experiments, performed with frogs, rabbits (see fig. 10) and cats, showed the drug had the general effect of dilating the vessels. In anaesthetized animals, injection of 2.5 mgm. (intravenously) causes a marked fall in blood pressure, which recovers quickly after a single dose (see fig. 11). If a number of such doses were administered, the blood pressure remained depressed. This fall in blood pressure was accompanied by an increased cardiac

output (see figs. 12 and 13), which was doubtless, in turn, due to the vasodilatation just described. On the pulmonary circulation, certain changes are produced which may be referred to the decided dilation of the coronary vessels already noted. For the first few minutes after injection, the right auricle pressure, the pulmonary pressure, the lung volume, and the left auricular pressure all increase, though not to any great extent; thus, 5 mgm. of Mitragynine only increase the pulmonary pressure by 10 mm. of half saturated sodium sulphate solution. The effect, however, was prolonged for several minutes. The probable explanation is

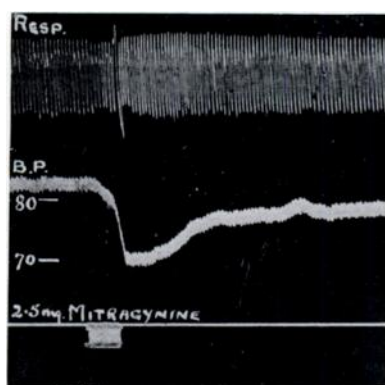


FIG. 11. CAT, URETHANE, BLOOD PRESSURE AND RESPIRATION. SHOWING THE EFFECT OF INJECTING 2.5 MGm. OF MITRAGYNINE HUMARATE

Time, 1 cm. = 32 seconds

as follows: The right auricular pressure is increased because a quantity of blood is short-circuited from the aorta to the right auricle by the dilated coronary vessels; this causes a rise in the pulmonary pressure since the right heart has to deal with more blood. The whole vascular volume of the lung is increased and more blood passes out from the pulmonary veins into the left auricle, so that the left auricular pressure also rises slightly. The output from the heart as a whole is very considerably increased; this, as has already been explained, is not due to any direct action of the drug on the heart. These points are illustrated in figures 14, 15 and 16. Mitragynine, then, in so far as the vascular

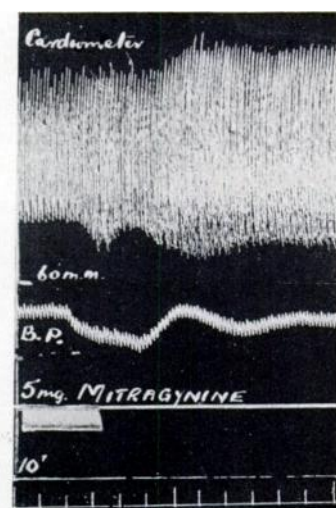


FIG. 12. CAT, AVERTIN, CARDIOMETER AND BLOOD PRESSURE. SHOWING THE EFFECT OF MITRAGYNINE FUMARATE



FIG. 13. CAT, A. C. E., URETHANE. TRACING OF AURICLE (UPPER) AND VENTRICLE (LOWER) AND BLOOD PRESSURE. SHOWING THE EFFECT OF INJECTING 5 MGM. OF MITRAGYNINE FUMARATE

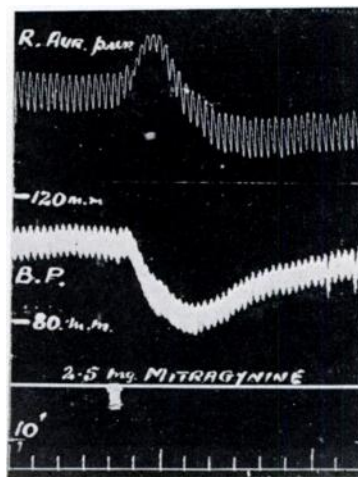


FIG. 14. CAT, A. C. E., URETHANE. RIGHT AURICULAR PRESSURE AND BLOOD PRESSURE. SHOWING THE EFFECT OF INJECTING 2.5 MGM. OF MITRAGYNINE FUMARATE

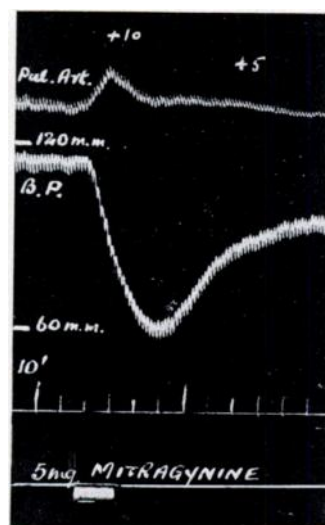


FIG. 15. CAT, A. C. E., URETHANE. PULMONARY ARTERY PRESSURE AND BLOOD PRESSURE. SHOWING THE EFFECT OF INJECTING 5 MGM. OF MITRAGYNINE FUMARATE

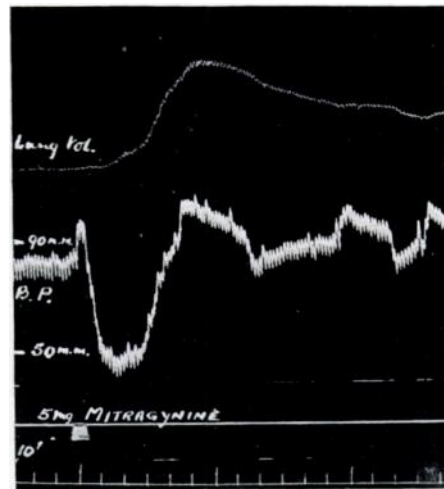


FIG. 16. CAT, A. C. E., URETHANE. LUNG VOLUME AND BLOOD PRESSURE. SHOWING THE EFFECT OF INJECTING 5 MGM. OF MITRAGYNINE FUMARATE

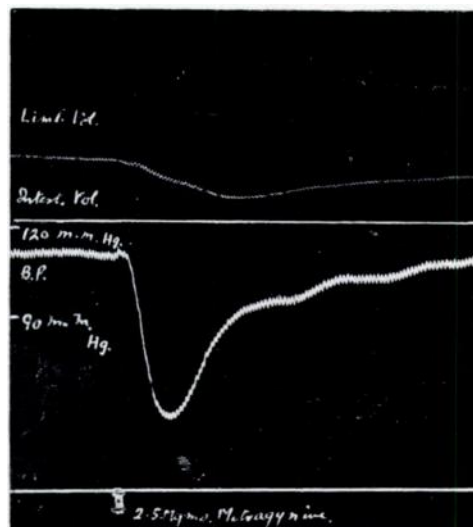


FIG. 17. CAT, URETHANE. LIMB VOLUME, INTESTINAL VOLUME AND BLOOD PRESSURE. SHOWING THE EFFECT OF INJECTING 2.5 MGM. OF MITRAGYNINE FUMARATE

system is concerned, may be said to exert its effect by dilating blood vessels (see fig. 17). It may be mentioned that blushing is a constant and marked effect which appears in man after administration of the drug.

ELECTROCARDIOGRAMS

During the experiments with perfused isolated hearts of frogs and rabbits, an effect was noticed to which reference has not yet

TABLE 5

Showing the effect of Mitragynine on rate, P-R interval and T wave of an electrocardiogram

INJECTION	RATE PER MINUTE	P-R INTERVAL	T WAVE
		<i>seconds</i>	
Before	132	0.08	Upright
I	138	0.08	Not quite so upright
II	132	0.1	Not quite so upright as before
III	138	0.11	Practically flat; right ventricle extrasystole
IV	150	0.11	Little; downward
V	168	0.11	As IV; no changes
VI	174	0.11	T wave little more downward
VII	186	0.11	Same as VI
VIII	156	0.11	T wave flat
IX	168	0.10	Same as VIII
X	156	0.10	Same as IX
XI	156	0.10	Same as X
XII	205	0.09	T wave downward
	168	0.10	T wave flat again
	162	0.09	Same as above

been made. This was the occurrence of heart block of a more or less severe degree. The matter was followed up by studying electrocardiographic records taken from an anaesthetised cat to which Mitragynine fumarate was administered by intravenous injection in 5 mgm. doses every five minutes. Each injection was followed, after an interval of one minute, by the taking of an electrocardiographic record. After 11 injections of 5 mgm., a twelfth injection of 10 mgm. was given, and further electrocardiograms were taken at intervals of one, four, and seven

minutes. The features of the electrocardiograms are given in table 5.

NERVOUS SYSTEM

Local anaesthetic effect

Laidlaw is quoted by Field (1) as having described the local anaesthetic action of Mitragynine. In the present investigation, therefore, the anaesthetic effect of Mitragynine on the rabbit's cornea was studied. Table 6 shows the results obtained. Mitragynine fumarate proved to be too irritating for use as a local anaesthetic of the human eye.

TABLE 6
Showing anaesthetic efficiency of Mitragynine fumarate on the rabbit's cornea

CONCENTRATION OF SOLUTION INSTILLED FOR 1 MINUTE	DURATION OF COMPLETE ANAESTHESIA	OTHER EFFECTS	
		Irritation	Changes in the cornea
<i>per cent</i> 1.0	<i>minutes</i> 42	Marked	Slightly hazy in 10 minutes; markedly hazy in 15 minutes; no permanent change
0.1	30	Slight	Dry and slightly hazy after 30 minutes; again clear in 1 hour; no permanent change
0.01	7	Very slight	No change

Peripheral nerves

The excitability and conduction of a frog's sciatic nerve is not affected by thirty minutes' immersion in a 1:1000 solution of Mitragynine. Painting the exposed sciatic nerve of an anaesthetised cat with Mitragynine does not lessen the rise of blood pressure which results from faradic stimulation of the nerve below the part treated with the drug.

Medulla

Mitragynine injected into rabbits, mice and frogs, gives an increase in the rate of respiration. If an animal be anaesthetised and the vagi be severed, stimulation of the central end of the

vagus will cause an alteration in the curve recording respiratory movements. The injection of Mitragynine lowers the threshold for faradic stimulation of the central end of the vagus (see fig. 18).

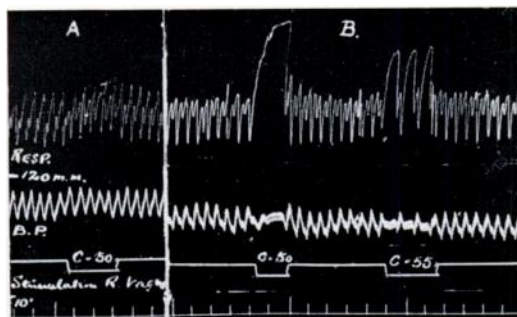


FIG. 18. CAT, A. C. E., CHLORALOSE. RESPIRATION AND BLOOD PRESSURE; VAGI CUT. SHOWING THE EFFECT ON RESPIRATION OF STIMULATION OF CENTRAL END OF RIGHT VAGUS

A, before, and B, after the injection of 4 mgm. of Mitragynine fumarate

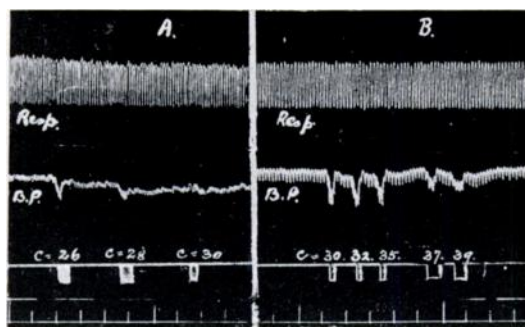


FIG. 19. RABBIT, ETHER URETHANE. RESPIRATION AND BLOOD PRESSURE; BOTH VAGI CUT. SHOWING THE EFFECT OF STIMULATION OF THE PERIPHERAL END OF RIGHT VAGUS BY A TETANIZING CURRENT A WITH THE SECONDARY COIL AT 26, 28, 30 CM. CONTROL AND B AFTER 5 MGM. OF MITRAGYNINE COIL AT 30, 32, 35, 37 AND 39 CM.

The rise in blood pressure which would normally be expected to follow such vagus stimulation, would here be masked by the vasodilatation due to the Mitragynine.

AUTONOMIC SYSTEM

It has already been pointed out that stimulation of the peripheral end of the vagus produces gut movements in the anaesthetised animal more readily after Mitragynine than before its ad-

TABLE 7
Cat; 3 kgm., A. C. E., urethane

	SEC. COIL DISTANCE (CMS.)	SECRETION
Stimulation of the chorda tympani for 10 seconds...	40	++
	42.5	+
	45.0	-
2.5 mgm. of Mitragynine injected into the jugular vein:		
1 minute after the injection.....	45.0	-
2 minutes after the injection.....	42.5	++
2½ minutes after the injection.....	43.5	++
3 minutes after the injection.....	45.0	+
4 minutes after the injection.....	46.0	-
2.5 mgm. of Mitragynine injected into the jugular vein:		
9 minutes after the injection.....	45.0	-
9½ minutes after the injection.....	43.5	-
10 minutes after the injection.....	42.5	-
14 minutes after the injection.....	42.5	-
15 minutes after the injection.....	40.0	-
16 minutes after the injection.....	38.0	-
17 minutes after the injection.....	36.0	+
18 minutes after the injection.....	36.0	++
24 minutes after the injection.....	38.0	+
25 minutes after the injection.....	40.0	+
26 minutes after the injection.....	45.0	-
27 minutes after the injection.....	42.5	-
28 minutes after the injection.....	40.0	+
5 mgm. of Mitragynine injected into the jugular vein:		
31 minutes after the injection.....	40.0	-
34 minutes after the injection.....	40.0	-
35 minutes after the injection.....	38.0	-
35 minutes after the injection.....	36.0	-
37 minutes after the injection.....	34.0	+

ministration. This facilitating action on the autonomic nervous system is manifest also in experiments performed on other organs. Figure 19 shows that a larger fall of blood pressure is obtained on stimulating the peripheral end of the cut vagus after

Mitragynine than before its administration. If the cat is anaesthetised with urethane, the chorda tympani exposed, and a cannula placed in the salivary duct, it is found, as table 7 shows, that weaker stimuli will produce a secretion of saliva after Mitragynine than before. If the cervical sympathetic nerves are exposed and stimulated in the neck, the pupil is dilated. It is found that the threshold of stimulation which will produce this effect is lowered by Mitragynine. Similarly, if arrangements are made to record bladder movements, the threshold for electric stimulation of the hypogastric nerve is lowered by Mitragynine, if the effect is judged by strength of stimulus necessary to produce contraction of the bladder. Finally, the pressor effect of splanchnic stimulation was found to be diminished by the administration of Mitragynine. Probably this result is due to the simultaneous vasodilatator action which the drug exerts.

In an animal (cat) the brain and cord of which have been destroyed, there is, immediately after the administration of Mitragynine, a smaller rise in blood pressure on the injection of 0.5 cc. of a 1:10,000 solution of adrenaline than was obtained before the drug was given.

GENERAL EFFECTS

The administration of Mitragynine in doses of 15 mgm. per kilogram body weight to rabbits, over a period of several weeks results in a progressive loss of weight and in deterioration of the coat, which in one case reached almost complete baldness. In rats, on a dose of 30 mgm. per kilogram body weight, there was obvious dulling of the coat, and patches of baldness.

TOXICITY

The minimal lethal dose of Mitragynine was determined for frogs, mice and rabbits. In the case of frogs and mice, the drug was dissolved in Ringer's solution. In the case of the rabbits it was given dissolved in water. Injections were made into the skin of the mouse, and under the skin of the rabbit. Minimal lethal doses found were as follows:

<i>Grams per kilogram</i>	
Frog.....	0.13
Mouse.....	{ 0.37 (subcutaneous)
	{ 0.20 (intraperitoneal)
Rabbit.....	0.13

The symptoms caused by administration of the drug are, in the frog, incoördination of movement, followed by paralysis and cessation of respiration. Dilation of the capillaries in the web of the foot can be observed. In the preliminary stages, there is an increase in reflexes. After a dose of 5 mgm. (about 0.25 grams per kilogram of body weight) death supervenes in about eight hours. In mammals (mice and rabbits) the main symptoms following large doses are exaggerated reflexes, tremors, muscular incoördination, struggling which sometimes amounts to convulsions, and finally, respiratory failure. In man, a 50 mgm. dose by the mouth produces motor excitement, followed by giddiness, Rombergism, and tremors of the extremities, face and tongue. These effects will be described more fully in a later communication.

GENERAL DISCUSSION

Mitragynine may be described as a general protozoal poison, in that it kills paramoecia at high dilution. Applied to isolated tissues, it has a general depressant effect. Thus, it diminishes the excitability of plain muscle, anaesthetises the cornea, and is toxic to animals in fairly low doses. In the first of these effects it resembles quinine. Examined in more detail, its actions on the nervous system may be considered under two headings. First, its effect on the autonomic system, which consists, apparently, in a facilitation of the passage of impulses, and which affects both the cranio-sacral and sympathetic divisions. Second, its action on the central nervous system, which consists in an increase in the excitability of the medulla, and probably of the motor centers. In this respect, it resembles cocaine. There is nothing to suggest that it is effective either as an antiseptic against bacteria or against pathogenic protozoa. The investigations here described do not assist us in explaining its action as a drug of addiction.

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